L4 ANSWER 36 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2001065863 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11087260
TITLE: Interaction between **angiotensin II** and Smad proteins in fibroblasts in failing heart and in vitro.
AUTHOR: Hao J; Wang B; Jones S C; Jassal D S; Dixon I M
CORPORATE SOURCE: Laboratory of Molecular Cardiology, Institute of Cardiovascular Sciences, St. Boniface General Hospital Research Centre, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada R2H 2A6.
SOURCE: American journal of physiology. Heart and circulatory physiology, (2000 Dec) 279 (6) H3020-30.
Journal code: 100901228. ISSN: 0363-6135.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001228

AB **Angiotensin II** (angiotensin) and transforming growth factor (TGF)-beta(1) play an important role in **cardiac fibrosis**. We examined Smad proteins in 8-wk post-myocardial infarction (MI) rat hearts. AT(1) blockade (losartan) attenuated the activation of TGF-beta(1) in target tissues. Losartan administration (8 wk, 15 mg. kg(-1). day(-1)) normalized total Smad 2 overexpression in infarct scar and remnant heart tissue and normalized Smad 4 in infarct scar. Phosphorylated Smad 2 (P-Smad 2) staining decreased in cytosol from failing heart vs. the control, which was normalized by losartan, suggesting augmented P-Smad 2 movement into nuclei in untreated failing hearts. Using adult primary rat fibroblasts treated with angiotensin (10(-6) M), we noted rapid translocation (15 min) of P-Smad 2 into the nuclei from the cytosol. Nuclear P-Smad 2 protein level increased with angiotensin treatment, which was blocked by losartan. We conclude that angiotensin may influence total Smad 2 and 4 expression in post-MI heart failure and that angiotensin treatment is associated with rapid P-Smad 2 nuclear translocation in isolated fibroblasts. This study suggests that cross talk between angiotensin and Smad signaling is associated with fibrotic events in post-MI hearts.

L4 ANSWER 35 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2002092072 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11821623
TITLE: The renin-angiotensin-aldosterone system and vascular remodeling.
AUTHOR: Sun Yao
CORPORATE SOURCE: Division of Cardiovascular Diseases, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN 38163, USA.. yasun@utmem.edu
SOURCE: Congestive heart failure (Greenwich, Conn.), (2002 Jan-Feb) 8 (1) 11-6. Ref: 56
Journal code: 9714174. ISSN: 1527-5299.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020201
Last Updated on STN: 20020404
Entered Medline: 20020403

AB **Cardiac fibrosis** can be accompanied initially by diastolic and ultimately by systolic ventricular dysfunction. Clinical and experimental evidence suggests a clear association between such adverse structural remodeling and activation of the circulating renin-angiotensin-aldosterone system (RAAS). Infusion of either of two RAAS effector hormones, **angiotensin II** and aldosterone, in rats evokes perivascular fibrosis of arteries and arterioles of the heart and kidneys. Additionally, increasing evidence indicates locally produced **angiotensin II** and aldosterone have important paracrine and autocrine actions that play a role in vascular remodeling. Both **angiotensin II** and aldosterone receptor antagonists have been shown to attenuate the appearance of cardiac and renal fibrosis.

L4 ANSWER 27 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2003169868 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12688405
TITLE: **Angiotensin II** type 1 receptor blocker, valsartan, prevented **cardiac fibrosis** in rat cardiomyopathy after autoimmune myocarditis.
AUTHOR: Tachikawa Hitoshi; Kodama Makoto; Hui Liu; Yoshida Tsuyoshi; Hayashi Manabu; Abe Satoru; Kashimura Takeshi; Kato Kiminori; Hanawa Haruo; Watanabe Kenichi; Nakazawa Mikio; Aizawa Yoshifusa
CORPORATE SOURCE: First Department of Internal Medicine, Niigata University Graduate School of Medicine, Niigata, Japan.. tachihh@med.niigata-u.ac.jp
SOURCE: Journal of cardiovascular pharmacology, (2003 Jan) 41 Suppl 1 S105-10.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030416
Last Updated on STN: 20030628
Entered Medline: 20030627

AB Favorable effects of **angiotensin II** type 1 receptor blockers on patients with ischemic or idiopathic dilated cardiomyopathy have already been suggested by several human trials but their effects on inflammatory cardiomyopathy remain unknown. We investigated the effects of the **angiotensin II** type 1 receptor blocker, valsartan, in chronic heart failure after inflammatory cardiomyopathy. Autoimmune myocarditis was induced in Lewis rats by injection with porcine cardiac myosin. In the phase of chronic heart failure, from day 28 until day 70, rats were treated by oral administration of valsartan. Three groups were designated: 1 ml saline, 10 mg/kg valsartan, and 30 mg/kg valsartan. On the 73rd day, hemodynamic parameters, pathological findings and the expression levels of r-ANP mRNA of the ventricle were examined, and were compared with the saline control. The ventricular weight/body weight ratio and area of fibrosis was decreased in the 30 mg/kg valsartan group. The left ventricular end-diastolic pressure and the central venous pressure were decreased in a dose-dependent manner in both valsartan groups, while the first pressure derivatives +dP/dt and -dP/dt did not differ among the three groups. A high dose of valsartan reduced the expression of tissue ANP mRNA compared with the saline group. In conclusion,valsartan suppressed myocardial hypertrophy and fibrosis, and it improved the hemodynamics and cardiac function in an animal model of post-myocarditis dilated cardiomyopathy.

L4 ANSWER 24 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2001154172 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11136485
TITLE: Aldosterone inhibition limits collagen synthesis and progressive left ventricular enlargement after anterior myocardial infarction.
COMMENT: Comment in: Am Heart J. 2001 Jan;141(1):1-2. PubMed ID: 11136478
AUTHOR: Modena M G; Aveta P; Menozzi A; Rossi R
CORPORATE SOURCE: Department of Cardiovascular Disease and Internal Medicine, Policlinico Hospital, University of Modena, Modena, Italy.. cardio@unimo.it
SOURCE: American heart journal, (2001 Jan) 141 (1) 41-6.
Journal code: 0370465. ISSN: 0002-8703.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010322

AB BACKGROUND: The reparative process after myocardial infarction is related to active collagen synthesis. Previous experimental studies demonstrated that **cardiac fibrosis** is mediated by **angiotensin II** and aldosterone; this mechanism is not clearly confirmed in patients who have had a myocardial infarction. The aim of this study was to evaluate whether the suppression of aldosterone may be helpful in reducing postinfarction collagen synthesis (and progressive left ventricular dilation) in patients treated with an angiotensin-converting enzyme inhibitor for a recent myocardial infarction. METHODS: We enrolled 46 patients (ages 60+/-11 years, 34 males) with a first episode of anterior transmural thrombolized myocardial infarction. At hospital discharge patients were randomized to receive potassium canrenoate, an oral aldosterone inhibitor, 50 mg once daily (group 1, n = 24) or placebo (group 2, n = 22). All enrolled patients were on angiotensin-converting enzyme inhibitor therapy. The serum concentration of the aminoterminal propeptide of type III procollagen was used to measure the collagen synthesis rate; dosage was obtained before enrollment, at hospital discharge, and after 3, 6, and 12 months of follow-up. RESULTS: After 3, 6, and 12 months of treatment, the aminoterminal propeptide of type III procollagen serum levels was significantly higher in the placebo group compared with the aldosterone inhibitor group; after 6 and 12 months we observed significantly smaller left ventricular volumes in the active treatment group. CONCLUSION: Potassium canrenoate, combined with an angiotensin-converting enzyme inhibitor, may reduce postinfarction collagen synthesis and progressive left ventricular dilation.

L4 ANSWER 22 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2003568222 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14642698
TITLE: Involvement of reactive oxygen species in **angiotensin II**-induced endothelin-1 gene expression in rat cardiac fibroblasts.
AUTHOR: Cheng Tzu-Hurng; Cheng Pao-Yun; Shih Neng-Lang; Chen Iuan-Bor; Wang Danny Ling; Chen Jin-Jer
CORPORATE SOURCE: Department of Medicine, Taipei Medical University-Wan Fang Hospital, and Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan.. thcheng@gate.sinica.edu.tw
SOURCE: Journal of the American College of Cardiology, (2003 Nov 19) 42 (10) 1845-54.
Journal code: 8301365. ISSN: 0735-1097.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040123
Entered Medline: 20040122

AB OBJECTIVES: The aim of this study was to investigate the effects of **angiotensin II** (Ang II) on fibroblast proliferation and endothelin-1 (ET-1) gene induction, focusing especially on reactive oxygen species (ROS)-mediated signaling in cardiac fibroblasts. BACKGROUND: **Angiotensin II** increases ET-1 expression, which plays an important role in Ang II-induced fibroblast proliferation. **Angiotensin II** also stimulates ROS generation in cardiac fibroblasts. However, whether ROS are involved in Ang II-induced proliferation and ET-1 expression remains unknown. METHODS: Cultured neonatal rat cardiac fibroblasts were stimulated with Ang II, and then [(3)H]thymidine incorporation and the ET-1 gene expression were examined. We also examined the effects of antioxidants on Ang II-induced proliferation and mitogen-activated protein kinase (MAPK) phosphorylation to elucidate the redox-sensitive pathway in fibroblast proliferation and ET-1 gene expression. RESULTS: Both AT(1) receptor antagonist (losartan) and ET(A) receptor antagonist (BQ485) inhibited Ang II-increased DNA synthesis. Endothelin-1 gene was induced with Ang II as revealed by Northern blotting and promoter activity assay. **Angiotensin II** increased intracellular ROS levels, which were inhibited with losartan and antioxidants. Antioxidants further suppressed Ang II-induced ET-1 gene expression, DNA synthesis, and MAPK phosphorylation. PD98059, but not SB203580, fully inhibited Ang II-induced ET-1 expression. Truncation and mutational analysis of the ET-1 gene promoter showed that AP-1 binding site was an important cis-element in Ang II-induced ET-1 gene expression. CONCLUSIONS: Our data suggest that ROS are involved in Ang II-induced proliferation and ET-1 gene expression. Our findings imply that the combination of AT(I) and ET(A) receptor antagonists plus antioxidants may be beneficial in preventing the formation of excessive **cardiac fibrosis**.

L4 ANSWER 20 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2001230200 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11304486
TITLE: Enhanced **angiotensin II** activity in heart failure: reevaluation of the counterregulatory hypothesis of receptor subtypes.
AUTHOR: Opie L H; Sack M N
CORPORATE SOURCE: Hatter Institute and Medical Research Council Inter-University Cape Heart Group, University of Cape Town Medical School, Cape Town, South Africa.. Opie@Capeheart.uct.ac.za
SOURCE: Circulation research, (2001 Apr 13) 88 (7) 654-8. Ref: 44
Journal code: 0047103. ISSN: 1524-4571.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010502
Last Updated on STN: 20010521
Entered Medline: 20010426

AB There are strong data favoring the pathogenic role of **angiotensin II** type 1 receptor (AT(1)) activation with subsequent promotion of myocyte growth and **cardiac fibrosis** in the development of cardiac hypertrophy and heart failure. An emerging hypothesis suggests that the activity of the **angiotensin II** type 2 receptor (AT(2)) may counterregulate AT(1) receptor effects during cardiac development and during the evolution of cardiac hypertrophy and heart failure. In this review, we examine the potential role of AT(2) activity in the context of this hypothesis. In contrast to the counterregulatory hypothesis, studies in mice with an overabundance of, or a deficiency in, the AT(2) receptor do not suggest that AT(2) signaling is essential for cardiac development. Moreover, the proposed antigrowth effects of AT(2) receptor signaling in pathological cardiac hypertrophy could not be shown in two mice models both deficient in AT(2) receptors. The role of AT(2) receptor signaling in **cardiac fibrosis** is, however, still debatable because of conflicting data in the same two studies. In **angiotensin II**-evoked apoptosis in cardiomyocytes, the proposed proapoptotic role of AT(2) activity could not be confirmed. Furthermore, in the progression from the bench to bedside, the results of two large clinical trials in heart failure, namely ELITE II and Val-HeFT, can be explained without ascribing a major protective role to the unopposed activity of the AT(2) receptor in the failing myocardium. In this review, we conclude that the collective evidence does not strongly support a net beneficial effect of AT(2) stimulation in the diseased myocardium.

L4 ANSWER 18 OF 83 MEDLINE on STN
ACCESSION NUMBER: 97338206 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9194767
TITLE: Prevention of aortic fibrosis by spironolactone in spontaneously hypertensive rats.
AUTHOR: Benetos A; Lacolley P; Safar M E
CORPORATE SOURCE: Department of Internal Medicine, Broussais Hospital, Paris, France.
SOURCE: Arteriosclerosis, thrombosis, and vascular biology, (1997 Jun) 17 (6) 1152-6.
Journal code: 9505803. ISSN: 1079-5642.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970721
Last Updated on STN: 19970721
Entered Medline: 19970710

AB We have previously shown that long-term angiotensin-converting enzyme (ACE) inhibition prevents the increase in aortic collagen in spontaneously hypertensive rats (SHRs), independent of blood pressure reduction. More recently, we reported that the effects of ACE inhibition in the prevention of aortic collagen accumulation were related to the inhibition of **angiotensin II** actions on **angiotensin II** type 1 receptors. Aldosterone, the synthesis of which is mainly modulated by **angiotensin II** through type 1 receptor stimulation, is known to promote **cardiac fibrosis** in different experimental models. The aim of the present study was to determine whether inhibition of aldosterone formation was able to prevent aortic fibrosis in SHRs. For this purpose, we compared the effects of a 4-month treatment with the aldosterone antagonist spironolactone with the ACE inhibitor quinapril in 4-week-old SHRs. Control SHRs and Wistar-Kyoto (WKY) rats received placebo for the same period of time. At the end of treatment, in conscious SHRs vs WKY controls, quinapril completely prevented the development of hypertension, whereas spironolactone produced only a slight but significant reduction in blood pressure. Aortic hypertrophy was significantly prevented by ACE inhibition but not by spironolactone. On the contrary, aortic collagen accumulation was completely prevented by both quinapril and spironolactone. In the latter case, collagen density was significantly below that of WKY controls. These results show that in SHRs, spironolactone can markedly prevent aortic fibrosis in the presence of a very slight antihypertensive effect. It is suggested that ACE inhibition or type 1 receptor antagonist-induced prevention of aortic collagen accumulation is at least partially related to aldosterone inhibition.

L4 ANSWER 17 OF 83 MEDLINE on STN
ACCESSION NUMBER: 1998137041 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9476560
TITLE: Assessment of the **angiotensin II** -forming pathway in human atria.
AUTHOR: Ohmichi N; Iwai N; Shimoike H; Izumi M; Watarida S; Mori A; Nakamura Y; Kinoshita M
CORPORATE SOURCE: First Department of Internal Medicine, Shiga University of Medical Sciences, Ohtsu, Japan.
SOURCE: Heart and vessels, (1997) Suppl 12 116-8.
Journal code: 8511258. ISSN: 0910-8327.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 20000303
Entered Medline: 19980407

AB A cardiac **angiotensin II**-generating system is thought to be involved in **cardiac fibrosis**. Both angiotensin-converting enzyme (ACE) and human chymase can convert angiotensin I to **angiotensin II**. However, the relative contributions of these two enzymatic pathways to **angiotensin II** generation in vivo remain to be clarified. In 31 patients with heart diseases, we assessed the expression levels of mRNAs for collagen type I-alpha, ACE, and chymase in right atrial appendages by competitive reverse transcriptional polymerase chain reaction and Northern blot analyses. The expression level of the ACE mRNA was about 100 times higher than that of the chymase mRNA. The collagen type I-alpha mRNA concentration was significantly and positively correlated with both the mean pulmonary arterial pressure ($r = 0.414$; $P = 0.020$) and the ACE mRNA concentration ($r = 0.548$; $P = 0.0014$). However, the chymase mRNA concentration was not correlated with the collagen type I-alpha mRNA concentration. Multivariate regression analysis revealed that the collagen type I-alpha mRNA concentration was related to the ACE mRNA concentration ($P = 0.0028$) and to the mean pulmonary arterial pressure ($P = 0.0386$) [$r = 0.633$, $P < 0.0008$]. The present results suggest that ACE may affect tissue **angiotensin II** levels in human atria. However, we obtained no evidence that chymase is important in determining tissue **angiotensin II** level.

L4 ANSWER 16 OF 83 MEDLINE on STN
ACCESSION NUMBER: 1998383536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9719054
TITLE: Early induction of transforming growth factor-beta via **angiotensin II** type 1 receptors contributes to **cardiac fibrosis** induced by long-term blockade of nitric oxide synthesis in rats.
AUTHOR: Tomita H; Egashira K; Ohara Y; Takemoto M; Koyanagi M; Katoh M; Yamamoto H; Tamaki K; Shimokawa H; Takeshita A
CORPORATE SOURCE: Research Institute of Angiocardiology and the Second Department of Internal Medicine, Kyushu University Faculty of Medicine, Fukuoka, Japan.
SOURCE: Hypertension, (1998 Aug) 32 (2) 273-9.
Journal code: 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980909

AB We previously reported that the chronic inhibition of nitric oxide (NO) synthesis increases cardiac tissue angiotensin-converting enzyme expression and causes **cardiac fibrosis** in rats. However, the mechanisms are not known. Transforming growth factor-beta (TGF-beta) is a key molecule that is responsible for tissue fibrosis. The present study investigated the role of TGF-beta in the pathogenesis of **cardiac fibrosis**. The development of **cardiac fibrosis** by oral administration of the NO synthesis inhibitor N(omega)-nitro-L-arginine methyl ester (L-NAME) to normal rats was preceded by increases in mRNA levels of cardiac TGF-beta1 and extracellular matrix (ECM) proteins. TGF-beta immunoreactivity was increased in the areas of fibrosis. Treatment with a specific **angiotensin II** type 1 receptor antagonist, but not with hydralazine, completely prevented the L-NAME-induced increases in the gene expression of TGF-beta1 and ECM proteins and also prevented **cardiac fibrosis**. Intraperitoneal injection of neutralizing antibody against TGF-beta did not affect the L-NAME-induced increase in TGF-beta1 mRNA levels but prevented an increase in the mRNA levels of ECM protein. These results suggest that the early induction of TGF-beta1 via the **angiotensin II** type 1 receptor plays a major role in the development of **cardiac fibrosis** in this model.

L4 ANSWER 13 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2000237485 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10773230
TITLE: **Angiotensin II**, adhesion, and **cardiac fibrosis**.
AUTHOR: Schnee J M; Hsueh W A
CORPORATE SOURCE: University of California-Los Angeles, School of Medicine, Division of Endocrinology, Diabetes, and Hypertension, Warren Hall, 2nd Floor, Rm 24-130, 900 Veteran Avenue, Mail Code 178622, Los Angeles, CA, USA.
SOURCE: Cardiovascular research, (2000 May) 46 (2) 264-8. Ref: 46
Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000622
Last Updated on STN: 20000622
Entered Medline: 20000612

AB **Angiotensin II** (AII) plays a critical role in cardiac remodeling. This peptide promotes cardiac myocyte hypertrophy and cardiac fibroblast interstitial fibrotic changes associated with left ventricular hypertrophy, post myocardial infarction remodeling and congestive heart failure. AII mediates cardiac myocyte hypertrophy directly via induction of immediate early genes through a MAP kinase dependent pathway. In addition, it mediates cardiac hypertrophy indirectly by stimulating release of norepinephrine from cardiac nerve endings and endothelin from endothelial cells. AII also has multiple effects on cardiac fibroblasts: it induces cardiac fibroblast proliferation, synthesis and secretion of adhesion molecules and extracellular matrix proteins, and expression of integrin adhesion receptors. In addition it stimulates cardiac fibroblasts to adhere more vigorously to defined matrixes. This review will discuss the molecular pathways that have been implicated in these AII induced effects in the cardiac fibroblast.

L4 ANSWER 11 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2000239323 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10779052
TITLE: **Angiotensin II**-induced cardiomyocyte hypertrophy and **cardiac fibrosis** in stroke-prone spontaneously hypertensive rats.
AUTHOR: Ikeda Y; Nakamura T; Takano H; Kimura H; Obata J E; Takeda S; Hata A; Shido K; Mochizuki S; Yoshida Y
CORPORATE SOURCE: Department of Internal Medicine, Yamanashi Medical University, Japan.
SOURCE: Journal of laboratory and clinical medicine, (2000 Apr) 135 (4) 353-9.
Journal code: 0375375. ISSN: 0022-2143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000509

AB Angiotensin-converting enzyme inhibitors (ACEIs) cause regression of hypertensive left ventricular hypertrophy (LVH) by reducing **angiotensin II**, increasing bradykinin, or both. The mechanisms of these cardioprotective effects remain controversial. The aims of this study were to determine whether the cardioprotective effects of ACEIs are mediated by reducing **angiotensin II** and whether ACEIs ameliorate the morphologic, physiologic, and biochemical changes in the hearts of stroke-prone spontaneously hypertensive rats (SHRSPs). Male SHRSPs were treated with hydralazine, captopril, or candesartan, an **angiotensin II** type 1 receptor (AT1R) antagonist, from age 12 to 24 weeks. We measured systolic blood pressure (SBP), left ventricular weight (LVW), left ventricular (LV) myocyte cross-sectional area (myocyte size), LV Interstitial collagen volume fraction (ICVF), perivascular collagen area/luminal area ratio (PVCA/LA), the medial area to luminal area ratio (MA/LA), the relative amount of V3 myosin heavy chain (MHCV3), and coronary reserve maximum (coronary flow max/ventricular weight (CFmax/VW)). These parameters were compared with those of untreated SHRSPs and Wistar-Kyoto rats (WKYs). SHRSPs exhibited decreased coronary reserve and LVH with an increase in myocyte size, PVCA/LA, MA/LA, and MHCV3 at 12 weeks of age. In addition to these changes, 24-week-old SHRSPs showed an increase in ICVF. The LVW, coronary reserve, myocyte size, PVCA/LA, ICVF, and MHCV3 of SHRSPs treated with captopril or candesartan all approached control values. In contrast, hydralazine decreased only ICVF. These results suggest that ACEIs regress LVH and normalize coronary reserve by modulating the effects of **angiotensin II** via AT1R on the induction of cardiomyocyte hypertrophy, perivascular fibrosis, and medial thickening of intramyocardial coronary arteries in SHRSPs. We concluded that these effects, in addition to the reduction of SBP, are important in causing the regression of LVH.

L4 ANSWER 8 OF 83 MEDLINE on STN
ACCESSION NUMBER: 1998217010 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9557931
TITLE: Angiotensin converting enzyme inhibition modulates cardiac fibroblast growth.
AUTHOR: Grohe C; Kahlert S; Lobbert K; Neyses L; van Eickels M; Stimpel M; Vetter H
CORPORATE SOURCE: Medizinische Universitats-Poliklinik, University of Bonn, Germany.. c.grohe@uni.bonn.de
SOURCE: Journal of hypertension, (1998 Mar) 16 (3) 377-84. Journal code: 8306882. ISSN: 0263-6352.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980625
Last Updated on STN: 19980625
Entered Medline: 19980616

AB BACKGROUND: The progression of left ventricular hypertrophy and **cardiac fibrosis** in hypertensive heart disease is influenced by sex and age. Although angiotensin converting enzyme inhibition has been shown to prevent progression of the disease in postmenopausal women, the interaction of **angiotensin II** and estrogen in this process before and after the menopause is poorly understood. OBJECTIVE: To investigate the influence of the angiotensin converting enzyme inhibitor moexiprilat on serum, estrogen and **angiotensin II**-induced cardiac fibroblast growth. METHODS: Neonatal rat cardiac fibroblasts were incubated with 1 and 10% fetal calf serum, 10(-7) mol/l **angiotensin II**, 10(-9) mol/l estrone, 10(-9) mol/l 17beta-estradiol and 10(-8) mol/l moexiprilat. Proliferation was measured in terms of incorporation of bromodeoxyuridine. Western blot analysis was performed using antibodies directed against the growth-related immediate early genes c-fos and Sp-1. All experiments were performed at least three times. RESULTS: Fetal calf serum stimulated cardiac fibroblast proliferation (1% fetal calf serum 2.0+/-0.028-fold; 10% fetal calf serum 2.7+/-0.028-fold). **Angiotensin II** and estrone stimulated proliferation of cardiac fibroblasts grown in the absence of fetal calf serum (**angiotensin II** 4.2+/-0.075-fold; estrone 2.9+/-0.034-fold) and further increased proliferation in the presence of 1% fetal calf serum (angiotensin 11 4.3+/-0.072-fold); estrone 3.8+/-0.045-fold) and 10% fetal calf serum ( **angiotensin II** 4.8+/-0.112-fold; estrone 4.1+/-0.047-fold). Coincubation with moexiprilat specifically inhibited proliferation induced by **angiotensin II** and estrone but not by serum, and **angiotensin II** type 1 receptor blockade inhibited **angiotensin II**-induced but not estrone-induced cell growth. Western blot analysis showed that the expression of c-fos and Sp-1 was induced in a time-dependent fashion by **angiotensin II** (to maxima of 5.0-fold for c-fos and 3.0-fold for Sp-1) and estrone (15.2-fold for c-fos and 6.2-fold for Sp-1). This effect was completely inhibited by moexiprilat. CONCLUSIONS: Angiotensin converting enzyme inhibition modulates cardiac fibroblast growth induced by **angiotensin II** and estrone. This mechanism might contribute to the beneficial effects of angiotensin converting enzyme inhibition in postmenopausal patients with hypertensive heart disease.

L4 ANSWER 7 OF 83 MEDLINE on STN
ACCESSION NUMBER: 96308191 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8701189
TITLE: [Left-ventricular hypertrophy as a cardiac risk factor: role of the renin-angiotensin-aldosterone system]. Linksventrikulare Hypertrophie als kardialer Risikofaktor: Die Rolle des Renin-Angiotensin-Aldosteron-Systems.
AUTHOR: Erne P
CORPORATE SOURCE: Abteilung Kardiologie, Kantonsspital Luzern.
SOURCE: Schweizerische Rundschau fur Medizin Praxis = Revue suisse de medecine Praxis, (1996 Feb 20) 85 (8) 227-33. Ref: 34
Journal code: 8403202. ISSN: 1013-2058.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960912
Last Updated on STN: 19970203
Entered Medline: 19960904

AB Left-ventricular hypertrophy is the result of cardiac adaptation to global or regional overstress and represents an important cardiovascular risk factor, increasing the risk for development of congestive heart failure and incidence of sudden death. This review describes the pathophysiological and biochemical mechanisms involved in the development of left-ventricular hypertrophy and **cardiac fibrosis** with particular emphasis on the role of **angiotensin II** and aldosterone. Central to the cascade of **cardiac fibrosis** is the increased production or reduced degradation of collagen proteins in fibroblasts. Collagen proteins are proteins needed for the alignment of cellular compartments and the development of forces, contraction and relaxation of the heart. If overexpressed, an important rise of wall stiffness is observed in addition to a reduced capacity to provide oxygen to the cardiac tissue. This latter explains why in areas of histologically hypertrophied heart muscle atrophied muscle cells are observed. The characterization of the second-messenger systems involved in the regulation of cardiac cells as well as the identification of **angiotensin-II** receptor subtype and angiotensin IV is described. Both of these receptors are present on cardiac fibroblasts and stimulate these to collagen production, which can be inhibited by antagonists or the generation of **angiotensin II** by ACE inhibitors. In some forms of left-ventricular hypertrophy and in patients with congestive heart failure in addition to elevated **angiotensin -II** levels, increased aldosterone levels are observed. Aldosterone raises upon stimulation by **angiotensin II** and upon reduction of **angiotensin-II** generation subsequent to ACE inhibition through an escape mechanism. The contribution of aldosterone to left-ventricular hypertrophy and **cardiac fibrosis** can be prevented and reduced by the administration of its antagonist, spironolactone. Further and larger clinical trials are needed and in progress to evaluate if the combination of an ACE inhibitor with spironolactone potentiates the reduction of left-ventricular hypertrophy and if this translates in a reduction of the cardiovascular risk.

L4 ANSWER 4 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2004268137 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15123578
TITLE: Role of osteopontin in **cardiac fibrosis** and remodeling in **angiotensin II** -induced cardiac hypertrophy.
COMMENT: Comment in: Hypertension. 2004 Jun;43(6):1164-5. PubMed ID: 15117918
AUTHOR: Matsui Yutaka; Jia Nan; Okamoto Hiroshi; Kon Shigeyuki; Onozuka Hisao; Akino Masatoshi; Liu Lizhi; Morimoto Junko; Rittling Susan R; Denhardt David; Kitabatake Akira; Uede Toshimitsu
CORPORATE SOURCE: Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan.
SOURCE: Hypertension, (2004 Jun) 43 (6) 1195-201.
Journal code: 7906255. ISSN: 1524-4563.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 20040529
Last Updated on STN: 20041029
Entered Medline: 20041028

AB Osteopontin (OPN) is upregulated in several experimental models of **cardiac fibrosis** and remodeling. However, its direct effects remain unclear. We examined the hypothesis that OPN is important for the development of **cardiac fibrosis** and remodeling. Moreover, we examined whether the inhibitory effect of eplerenone (Ep), a novel aldosterone receptor antagonist, was mediated through the inhibition of OPN expression against **cardiac fibrosis** and remodeling. Wild-type (WT) and OPN-deficient mice were treated with **angiotensin II** (Ang II) for 4 weeks. WT mice receiving Ang II were divided into 2 groups: a control group and an Ep treatment group. Ang II treatment significantly elevated blood pressure and caused cardiac hypertrophy and fibrosis in WT mice. Ep treatment and OPN deficiency could reduce the Ang II-induced elevation of blood pressure and ameliorate the development of **cardiac fibrosis**, whereas Ep-only treatment abolished the development of cardiac hypertrophy. Most compelling, the reduction of **cardiac fibrosis** led to an impairment of cardiac systolic function and subsequent left ventricular dilatation in Ang II-treated OPN-deficient mice. These results suggest that OPN has a pivotal role in the development of Ang II-induced **cardiac fibrosis** and remodeling. Moreover, the effect of Ep on the prevention of **cardiac fibrosis**, but not cardiac hypertrophy, might be partially mediated through the inhibition of OPN expression.

L4 ANSWER 3 OF 83 MEDLINE on STN
ACCESSION NUMBER: 96066715 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7593636
TITLE: **Angiotensin II**-induced **cardiac fibrosis** in the rat is increased by chronic inhibition of nitric oxide synthase.
AUTHOR: Hou J; Kato H; Cohen R A; Chobanian A V; Brecher P
CORPORATE SOURCE: Department of Biochemistry, Boston University School of Medicine, Massachusetts 02118, USA.
CONTRACT NUMBER: HL-47124 (NHLBI)
SOURCE: Journal of clinical investigation, (1995 Nov) 96 (5) 2469-77.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951221

AB These studies were performed to determine if the effects of **angiotensin II** infusion on the development of **cardiac fibrosis** could be modified by the chronic inhibition of nitric oxide synthase activity. NG-nitro-L-arginine-methyl ester (L-NAME) was administered to adult Wistar rats in drinking water (40 mg/kg per d). Although blood pressure was maintained at hypertensive levels after 2 wk, cardiac hypertrophy or fibrosis did not occur. **Angiotensin II**, given for 3 d at a dose which induced little or no blood pressure elevation and minimal if any fibrosis, caused significant fibrosis when given to a rat pretreated for 2 wk with L-NAME. This marked fibrosis did not occur if **angiotensin II** was given shortly after L-NAME treatment was begun or briefly after discontinuation of L-NAME. The fibrosis that occurred with combined treatment was characterized by increased immunodetectable fibronectin, the presence of inflammatory cells within interstitial and perivascular regions, and increased steady state mRNA levels for matrix genes and atrial natriuretic protein. The data indicated a regulatory role for nitric oxide in modulating the **angiotensin II**-induced **cardiac fibrosis** and suggest a potentially important autocrine or paracrine role for nitric oxide in fibroblast proliferation.

L4 ANSWER 2 OF 83 MEDLINE on STN
ACCESSION NUMBER: 1998034185 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9369252
TITLE: Effect of nitric oxide on DNA replication induced by **angiotensin II** in rat cardiac fibroblasts.
AUTHOR: Takizawa T; Gu M; Chobanian A V; Brecher P
CORPORATE SOURCE: Department of Biochemistry and The Cardiovascular Institute, Boston University School of Medicine, Mass 02118, USA.
SOURCE: Hypertension, (1997 Nov) 30 (5) 1035-40.
Journal code: 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971210

AB Our previous in vivo studies (Hou et al. J Clin Invest. 1995;96:2469-2477.) demonstrated that chronic inhibition of nitric oxide synthase led to an exaggerated response to relatively low doses of **angiotensin II**, resulting in a rapid and marked **cardiac fibrosis**. To examine further the importance of **angiotensin II** in inducing **cardiac fibrosis** and the possibility that nitric oxide serves as a modulator of the proliferative effects of **angiotensin II**, we used cultured rat cardiac fibroblasts to study the interrelationships between these substances. **Angiotensin II** induced a delayed DNA synthetic response in quiescent cells that occurred 30 hours after exposure to the hormone. The most pronounced effect of **angiotensin II** on thymidine uptake occurred 36 to 42 hours after the addition to cells. This response was inhibited in a dose-dependent manner by the addition of either S-nitroso-N-acetylpenicillamine or sodium nitroprusside, each a source of nitric oxide. The nitric oxide donor was most effective in reducing thymidine incorporation when added 12 hours after **angiotensin II**, whereas the metabolite N-acetylpenicillamine had no effect at any time. The inhibitory effect of S-nitroso-N-acetylpenicillamine was mimicked by 8-bromoguanosine 3':5'-cyclic monophosphate but not by 8-bromoadenosine 3':5'-cyclic monophosphate. Nitric oxide donors did not appear to inhibit the induction of c-fos, Egr-1, or other immediate-early genes in response to **angiotensin II**. The results suggest that nitric oxide affects the cell cycle following the transition into G, and modulates the proliferation of fibroblasts during **cardiac fibrosis** induced by **angiotensin II**.

L4 ANSWER 1 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2002495321 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12356639
TITLE: Iron overload augments **angiotensin II** -induced **cardiac fibrosis** and promotes neointima formation.
AUTHOR: Ishizaka Nobukazu; Saito Kan; Mitani Haruo; Yamazaki Ieharu; Sata Masataka; Usui Shin-ichi; Mori Ichiro; Ohno Minoru; Nagai Ryozo
CORPORATE SOURCE: Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine, Japan.. nobuishizka-tky@umin.ac.jp
SOURCE: Circulation, (2002 Oct 1) 106 (14) 1840-6.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20021002
Last Updated on STN: 20021026
Entered Medline: 20021024

AB BACKGROUND: Abnormal iron deposition may cause oxidant-induced damage in various organs. We have previously reported that continuous administration of **angiotensin II** to rats results in an overt iron deposition in the renal tubular epithelial cells, which may have a role in **angiotensin II**-induced renal damage. In the present study, we investigated the role of iron in the development of cardiac injury induced by **angiotensin II**. METHODS AND RESULTS: **Angiotensin II** was continuously infused to rats at a dose of 0.7 mg/kg per day for 7 consecutive days. No iron deposits were observed in the hearts of untreated rats, whereas iron deposition was seen in the cells in the subepicardial and granulation regions after **angiotensin II** infusion. Concomitant administration of deferoxamine, an iron chelator, significantly reduced the extent of **cardiac fibrosis**, which suggests that iron deposition aggravates the **cardiac fibrosis** induced by **angiotensin II**. Iron overload caused by the administration of iron-dextran resulted in an augmentation of **cardiac fibrosis** and the generation of neointimal cells in the coronary artery in **angiotensin II**-infused rats. By contrast, neointima was not formed in the cardiac vessels in norepinephrine-infused rats with iron overload. CONCLUSIONS: Cardiac iron deposition may be involved in the development of **cardiac fibrosis** induced by **angiotensin II**. In addition, iron overload may enhance the formation of neointima under conditions of increased circulating **angiotensin II** but not catecholamines.

L7 ANSWER 18 OF 46 MEDLINE on STN
ACCESSION NUMBER: 2001635120 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11346891
TITLE: Induction of **cardiac fibrosis** by **angiotensin II**.
AUTHOR: Lijnen P J; Petrov V V; Fagard R H
CORPORATE SOURCE: Hypertension and Cardiovascular Rehabilitation Unit, Department of Molecular and Cardiovascular Research, Faculty of Medicine, University of Leuven, Leuven, Belgium.. paul.lijnen@med.kuleuven.ac.be
SOURCE: Methods and findings in experimental and clinical pharmacology, (2000 Dec) 22 (10) 709-23. Journal code: 7909595. ISSN: 0379-0355.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200111
ENTRY DATE: Entered STN: 20011105
Last Updated on STN: 20011105
Entered Medline: 20011101

AB The possible contributions of the angiotensin receptor subtypes 1 (AT1) and 2 (AT2) to **angiotensin II**-induced changes in **collagen** secretion and production were studied using the specific angiotensin receptor AT1 and AT2 antagonists telmisartan and P-186. The role of the renin-angiotensin system and its interaction with transforming growth factor-beta 1 (TGF-beta 1) in **collagen** deposition in cardiac fibroblasts in relation to the development of myocardial fibrosis is also discussed. Cardiac fibroblasts (from normal male adult rats) from passage 2 were cultured to confluency and incubated in the presence of **angiotensin II** (ANG II) in a concentration range of 10(-10)-10(-6) M in serum-free Dulbecco's MEM medium for 24 h. **Collagen** production and secretion were assayed by [3H]-proline incorporation and noncollagen production and secretion were also analyzed. ANG II dose-dependently increased **collagen** secretion and production in rat adult cardiac fibroblasts in culture. Noncollagen secretion and production were also concentration-dependently increased by ANG II. Addition of 100 nmol/l ANG II increased ($p < 0.01$) **collagen** secretion and production by 75 +/- 6 (SEM) and 113 +/- 23%, respectively, and noncollagen secretion and production by 65 +/- 6 and 57 +/- 16%, respectively. Pretreatment of cardiac fibroblasts with telmisartan completely blocked the ANG II-induced increase in **collagen** secretion ($p < 0.001$) and production ($p < 0.05$) and in noncollagen secretion ($p < 0.01$) and production ($p < 0.01$). P-186 had no effect on the ANG II-induced increase in **collagen** secretion and production. Addition of telmisartan and P-186 did not affect **collagen** secretion and production in basal cardiac fibroblasts. TGF-beta 1 also concentration- and time-dependently increased the secretion and production of **collagen** in cardiac fibroblasts. Our data demonstrate that the effects of ANG II on **collagen** secretion and production in adult rat cardiac fibroblasts in culture are AT1-receptor mediated since they were abolished by the specific AT1-receptor antagonist telmisartan but not by the specific AT2-receptor antagonist P-186. The ability of ANG II to induce **collagen** synthesis in cardiac fibroblasts may be mediated by increased TGF-beta 1 production.

L7 ANSWER 19 OF 46 MEDLINE on STN
ACCESSION NUMBER: 2001478834 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11522607
TITLE: Effects of ACE inhibition and **angiotensin II** type 1 receptor blockade on cardiac function and G proteins in rats with chronic heart failure.

AUTHOR: Yoshida H; Takahashi M; Tanonaka K; Maki T; Nasa Y; Takeo S
CORPORATE SOURCE: Department of Pharmacology, Tokyo University of P

L7 ANSWER 29 OF 46 MEDLINE on STN
ACCESSION NUMBER: 2000239323 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10779052
TITLE: **Angiotensin II**-induced cardiomyocyte hypertrophy and **cardiac fibrosis** in stroke-prone spontaneously hypertensive rats.
AUTHOR: Ikeda Y; Nakamura T; Takano H; Kimura H; Obata J E; Takeda S; Hata A; Shido K; Mochizuki S; Yoshida Y
CORPORATE SOURCE: Department of Internal Medicine, Yamanashi Medical University, Japan.
SOURCE: Journal of laboratory and clinical medicine, (2000 Apr) 135 (4) 353-9.
Journal code: 0375375. ISSN: 0022-2143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000509

AB Angiotensin-converting enzyme inhibitors (ACEIs) cause regression of hypertensive left ventricular hypertrophy (LVH) by reducing **angiotensin II**, increasing bradykinin, or both. The mechanisms of these cardioprotective effects remain controversial. The aims of this study were to determine whether the cardioprotective effects of ACEIs are mediated by reducing **angiotensin II** and whether ACEIs ameliorate the morphologic, physiologic, and biochemical changes in the hearts of stroke-prone spontaneously hypertensive rats (SHRSPs). Male SHRSPs were treated with hydralazine, captopril, or candesartan, an **angiotensin II** type 1 receptor (AT1R) antagonist, from age 12 to 24 weeks. We measured systolic blood pressure (SBP), left ventricular weight (LVW), left ventricular (LV) myocyte cross-sectional area (myocyte size), LV Interstitial **collagen** volume fraction (ICVF), perivascular **collagen** area/luminal area ratio (PVCA/LA), the medial area to luminal area ratio (MA/LA), the relative amount of V3 myosin heavy chain (MHCV3), and coronary reserve maximum (coronary flow max/ventricular weight (CFmax/VW)). These parameters were compared with those of untreated SHRSPs and Wistar-Kyoto rats (WKYs). SHRSPs exhibited decreased coronary reserve and LVH with an increase in myocyte size, PVCA/LA, MA/LA, and MHCV3 at 12 weeks of age. In addition to these changes, 24-week-old SHRSPs showed an increase in ICVF. The LVW, coronary reserve, myocyte size, PVCA/LA, ICVF, and MHCV3 of SHRSPs treated with captopril or candesartan all approached control values. In contrast, hydralazine decreased only ICVF. These results suggest that ACEIs regress LVH and normalize coronary reserve by modulating the effects of **angiotensin II** via AT1R on the induction of cardiomyocyte hypertrophy, perivascular fibrosis, and medial thickening of intramyocardial coronary arteries in SHRSPs. We concluded that these effects, in addition to the reduction of SBP, are important in causing the regression of LVH.

L7 ANSWER 30 OF 46 MEDLINE on STN
ACCESSION NUMBER: 2000029683 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10562266
TITLE: **Angiotensin II** type 1A receptor knockout mice display less left ventricular remodeling and improved survival after myocardial infarction

L7 ANSWER 30 OF 46 MEDLINE on STN
ACCESSION NUMBER: 2000029683 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10562266
TITLE: **Angiotensin II** type 1A receptor knockout mice display less left ventricular remodeling and improved survival after myocardial infarction.
COMMENT: Comment in: Circulation. 1999 Nov 16;100(20):2043-4. PubMed ID: 10562257
AUTHOR: Harada K; Sugaya T; Murakami K; Yazaki Y; Komuro I
CORPORATE SOURCE: Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine.
SOURCE: Circulation, (1999 Nov 16) 100 (20) 2093-9.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20010521
Entered Medline: 19991207

AB BACKGROUND: **Angiotensin II** (Ang II) has been implicated in ventricular remodeling after myocardial infarction (MI), which is an important determinant for prognosis after MI. The aim of this study was to determine whether Ang II type 1A receptor (AT(1A))-mediated Ang II signals are critically involved in the mortality and LV remodeling after MI. METHODS AND RESULTS: We examined survival, cardiac geometry and function, **cardiac fibrosis**, and gene expression of AT(1A) knockout (KO) mice and wild-type (WT) mice at 1 and 4 weeks after large MI. The survival rate was higher in KO mice than in WT mice at 4 weeks after MI. All WT survivors showed severe heart failure, detected by marked increases in both RV weight and lung weight. LV remodeling, such as the development of LV dilatation, LV dysfunction, and **cardiac fibrosis** at the noninfarcted area, were comparable in both kinds of mice at 1 week after MI. At 4 weeks after MI, however, WT mice showed more marked remodeling than KO mice. mRNA levels of AT(1) at the noninfarcted area were increased from 1 to 4 weeks after MI only in WT mice, whereas levels of AT(2) were not changed by MI in either kind of mouse. Accompanied by the development of geometric and structural remodeling, expression of fetal-type genes, **collagen**, and transforming growth factor-beta(1) genes were upregulated and sustained in the noninfarcted area of WT hearts. In contrast, they were rapidly downregulated to basal levels at 4 weeks after MI in that of KO hearts. CONCLUSIONS: These results indicate that AT(1A) signals play a pivotal role in the progression of LV remodeling after MI, resulting in overt heart failure.

L4 ANSWER 23 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2000385959 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10881748
TITLE: Mechanism of **cardiac fibrosis** by angiotensin. New insight revealed by genetic engineering.
AUTHOR: Matsusaka T; Katori H; Homma T; Ichikawa I
CORPORATE SOURCE: Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, USA.
CONTRACT NUMBER: DK-37868 (NIDDK)
DK-44757 (NIDDK)
SOURCE: Trends in cardiovascular medicine, (1999 Oct) 9 (7) 180-4.
Ref: 33
Journal code: 9108337. ISSN: 1050-1738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000809

AB Accumulating data show that excess of **angiotensin II** (Ang II) is involved in **cardiac fibrosis**. Many experimental studies suggested that Ang II induces **cardiac fibrosis** not by its blood pressure-raising action, but rather by a direct action on the heart. However, it has been difficult to distinguish the local and systemic actions in vivo. Recent genetic technology sheds new light on this problem. This review focuses on the recent advances and newly arising issues regarding the mechanism of Ang II-induced **cardiac fibrosis**.

L4 ANSWER 5 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2003086951 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12598081
TITLE: **Cardiac fibrosis** occurs early and involves endothelin and AT-1 receptors in hypertension due to endogenous **angiotensin II**.
AUTHOR: Seccia Teresa M; Belloni Anna S; Kreutz Reinhold; Paul Martin; Nussdorfer Gastone G; Pessina Achille C; Rossi Gian Paolo
CORPORATE SOURCE: Department of Clinical Methodology and Clinical-Surgical Technologies, University of Bari, Bari, Italy.
SOURCE: Journal of the American College of Cardiology, (2003 Feb 19) 41 (4) 666-73.
Journal code: 8301365. ISSN: 0735-1097.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030225
Last Updated on STN: 20030313
Entered Medline: 20030312

AB OBJECTIVES: We investigated if endothelin (ET)-1 and the renin-angiotensin-aldosterone system play a role in **cardiac fibrosis**. BACKGROUND: **Angiotensin II** (Ang II) can induce **cardiac fibrosis**, but the underlying mechanisms are incompletely understood. METHODS: Four-week-old transgenic (mRen2)27 rat (TGRen2) received for four weeks a placebo, the mixed ET(A)/ET(B) endothelin receptor antagonist bosentan, the **angiotensin II** type I receptor (AT-1) antagonist irbesartan, the ET(A) endothelin receptor antagonist BMS-182874, and a combined treatment with irbesartan plus BMS-182874. We measured collagen density on Sirius red-stained serial sections of the left ventricle (LV) with a photomicroscope equipped with specific software and assessed the gene expression of procollagen alpha1(I), atrial natriuretic peptide (ANP), transforming growth factor-beta 1 (TGFbeta1), endothelin converting enzyme, and ET(B) receptor. RESULTS: In the placebo group, hypertension was associated with LV hypertrophy and **cardiac fibrosis** (LV weight: 4.0 +/- 0.3 mg/g body weight; collagen density: 2.21 +/- 0.16%), which were all prevented with irbesartan (2.3 +/- 0.1, 1.30 +/- 0.13, $p < 0.001$), but not with BMS-182874 (4.0 +/- 0.2, 2.41 +/- 0.22). Bosentan also prevented fibrosis (1.39 +/- 0.18) but not hypertension and LV hypertrophy (3.38 +/- 0.27). Combined irbesartan and BMS-182874 treatment prevented LV hypertrophy (2.9 +/- 0.1) but not fibrosis (2.52 +/- 0.16). Collagen density correlated ($r = 0.414$, $p < 0.05$) with plasma aldosterone levels. In TGRen2 with LV hypertrophy, the gene expression of ANP and ET(B) but not that of TGFbeta1 and procollagen alpha1(I) was increased. CONCLUSIONS: In Ang II-dependent hypertension, **cardiac fibrosis** was associated with LV hypertrophy and was hindered by both mixed ET(A)/ET(B) blockade and AT-1 blockade. Only the latter treatment prevented both hypertension and LV hypertrophy. Thus, there is a dissociation between the mechanisms of **cardiac fibrosis** and hypertension, which do and do not entail ET-1, respectively.

L4 ANSWER 6 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2001406107 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11457756
TITLE: **Angiotensin II** type 2 receptor is essential for left ventricular hypertrophy and **cardiac fibrosis** in chronic **angiotensin II**-induced hypertension.
COMMENT: Comment in: Circulation. 2001 Jul 17;104(3):247-8. PubMed ID: 11457738
AUTHOR: Ichihara S; Senbonmatsu T; Price E Jr; Ichiki T; Gaffney F A; Inagami T
CORPORATE SOURCE: Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.
CONTRACT NUMBER: DK-20593 (NIDDK)
HL-58205 (NHLBI)
SOURCE: Circulation, (2001 Jul 17) 104 (3) 346-51.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB BACKGROUND: The roles of **angiotensin II** (Ang II) in the regulation of heart function under normal and pathological conditions have been well documented. Although 2 types of Ang II receptor (AT(1) and AT(2)) are found in various proportions, most studies have focused on AT(1)-coupled events. In the present study, we examined the hypothesis that signaling by AT(2) is important to the development of left ventricular hypertrophy and **cardiac fibrosis** by Ang II infusion in mice lacking the AT(2) gene (Agtr2-/Y). METHODS AND RESULTS: Male Agtr2-/Y and age-matched wild-type (WT) mice were treated long-term with Ang II, infused at a rate of 4.2 ng. kg(-1). min(-1) for 3 weeks. Ang II elevated systolic blood pressure to comparable levels in Agtr2-/Y and WT mice. WT mice developed prominent concentric cardiac hypertrophy, prominent fibrosis, and impaired diastolic relaxation after Ang II infusion. In contrast, there was no cardiac hypertrophy in Agtr2-/Y mice. Agtr2-/Y mice, however, did not show signs of heart failure or impairment of ventricular relaxation and only negligible fibrosis after Ang II infusion. The absence of fibrosis may be a clue to the absence of impairment in ventricular relaxation and account for the normal left ventricular systolic and diastolic performances in Agtr2-/Y mice. CONCLUSIONS: Chronic loss of AT(2) by gene targeting abolished left ventricular hypertrophy and **cardiac fibrosis** in mice with Ang II-induced hypertension.

L4 ANSWER 10 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2001635120 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11346891
TITLE: Induction of **cardiac fibrosis** by **angiotensin II**.
AUTHOR: Lijnen P J; Petrov V V; Fagard R H
CORPORATE SOURCE: Hypertension and Cardiovascular Rehabilitation Unit, Department of Molecular and Cardiovascular Research, Faculty of Medicine, University of Leuven, Leuven, Belgium.. paul.lijnen@med.kuleuven.ac.be
SOURCE: Methods and findings in experimental and clinical pharmacology, (2000 Dec) 22 (10) 709-23. Journal code: 7909595. ISSN: 0379-0355.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200111
ENTRY DATE: Entered STN: 20011105
Last Updated on STN: 20011105
Entered Medline: 20011101

AB The possible contributions of the angiotensin receptor subtypes 1 (AT1) and 2 (AT2) to **angiotensin II**-induced changes in collagen secretion and production were studied using the specific angiotensin receptor AT1 and AT2 antagonists telmisartan and P-186. The role of the renin-angiotensin system and its interaction with transforming growth factor-beta 1 (TGF-beta 1) in collagen deposition in cardiac fibroblasts in relation to the development of myocardial fibrosis is also discussed. Cardiac fibroblasts (from normal male adult rats) from passage 2 were cultured to confluency and incubated in the presence of **angiotensin II** (ANG II) in a concentration range of 10(-10)-10(-6) M in serum-free Dulbecco's MEM medium for 24 h. Collagen production and secretion were assayed by [3H]-proline incorporation and noncollagen production and secretion were also analyzed. ANG II dose-dependently increased collagen secretion and production in rat adult cardiac fibroblasts in culture. Noncollagen secretion and production were also concentration-dependently increased by ANG II. Addition of 100 nmol/l ANG II increased ($p < 0.01$) collagen secretion and production by 75 +/- 6 (SEM) and 113 +/- 23%, respectively, and noncollagen secretion and production by 65 +/- 6 and 57 +/- 16%, respectively. Pretreatment of cardiac fibroblasts with telmisartan completely blocked the ANG II-induced increase in collagen secretion ($p < 0.001$) and production ($p < 0.05$) and in noncollagen secretion ($p < 0.01$) and production ($p < 0.01$). P-186 had no effect on the ANG II-induced increase in collagen secretion and production. Addition of telmisartan and P-186 did not affect collagen secretion and production in basal cardiac fibroblasts. TGF-beta 1 also concentration- and time-dependently increased the secretion and production of collagen in cardiac fibroblasts. Our data demonstrate that the effects of ANG II on collagen secretion and production in adult rat cardiac fibroblasts in culture are AT1-receptor mediated since they were abolished by the specific AT1-receptor antagonist telmisartan but not by the specific AT2-receptor antagonist P-186. The ability of ANG II to induce collagen synthesis in cardiac fibroblasts may be mediated by increased TGF-beta 1 production.

L4 ANSWER 49 OF 83 MEDLINE on STN
ACCESSION NUMBER: 1999060165 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9843462
TITLE: Expression of functional angiotensin-converting enzyme and AT1 receptors in cultured human cardiac fibroblasts.
AUTHOR: Hafizi S; Wharton J; Morgan K; Allen S P; Chester A H; Catravas J D; Polak J M; Yacoub M H
CORPORATE SOURCE: Department of Cardiothoracic Surgery, National Heart and Lung Institute, Imperial College School of Medicine at the Heart Science Centre, Harefield Hospital, Middlesex, UK.
SOURCE: Circulation, (1998 Dec 8) 98 (23) 2553-9.
Journal code: 0147763. ISSN: 0009-7322.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19990104

AB BACKGROUND: **Angiotensin II** (Ang II) has been implicated in the development of **cardiac fibrosis**. The aims of the present study were to examine expression and activity of ACE and of angiotensin receptors in human cardiac fibroblasts cultured from dilated cardiomyopathic and ischemic hearts. The effects of Ang II on fibroblasts were also investigated. METHODS AND RESULTS: Human cardiac fibroblasts were cultured from ventricular and atrial myocardium and characterized immunohistochemically. Expression of ACE and the angiotensin AT1 receptor was demonstrated in cardiac fibroblasts by reverse transcriptase-polymerase chain reaction and radioligand binding. Functional ACE activity, measured by radiolabeled substrate conversion assay, was detected in both ventricular (Vmax. Km-1. mg-1, 0.031+/-0.010; n=13) and atrial (0. 034+/-0.012; n=6) fibroblasts. Fibroblast ACE activity was increased after 48 hours of treatment with basic fibroblast growth factor, dexamethasone, and phorbol ester. Ang II did not affect DNA synthesis but stimulated [3H]proline incorporation in cardiac fibroblasts (20.0+/-4.0% increase above control by 10 micromol/L; P<0.05, n=7), which was abolished by losartan 10 micromol/L but not PD123319 1 micromol/L. Ang II also stimulated a rise in intracellular calcium (basal, 56+/-1 nmol/L; Ang II, 355+/-24 nmol/L) via the AT1 receptor, as shown by complete inhibition with losartan. CONCLUSIONS: We have demonstrated expression and activity of ACE and AT1 receptor in cultured human cardiac fibroblasts. In addition, cardiac fibroblasts respond to Ang II with AT1 receptor-mediated collagen synthesis. The presence of local ACE and AT1 receptors in human fibroblasts suggests their involvement in the development of **cardiac fibrosis**.

L4 ANSWER 50 OF 83 MEDLINE on STN

L4 ANSWER 47 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2002172172 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11904534
TITLE: Tissue Angiotensin-converting enzyme activity plays an important role in pressure overload-induced **cardiac fibrosis** in rats.
AUTHOR: Kurosawa Yukie; Katoh Makoto; Doi Hisayoshi; Narita Hiroshi
CORPORATE SOURCE: Discovery Research Laboratory, Tanabe Seiyaku Co., Ltd., 2-2-50 Kawagishi, Toda-shi, Saitama 335-8505, Japan.
SOURCE: Journal of cardiovascular pharmacology, (2002 Apr) 39 (4) 600-9.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
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AB It has been widely assumed that the cardiac angiotensin-generating system plays an important role in the development and maintenance of cardiac remodeling caused by pressure overload. The roles of angiotensin-converting enzyme (ACE) in pressure overload-induced cardiac hypertrophy and fibrosis in rats were investigated. Pressure overload was achieved by constricting the abdominal aorta above the renal arteries. After they underwent surgery, the rats were treated with a low or high dose of the ACE inhibitor imidapril (0.07 and 0.7 mg/kg/d s.c.) with an osmotic pump for 4 weeks. High-dose imidapril prevented the increase in blood pressure, cardiac hypertrophy, and fibrosis. Low-dose imidapril inhibited only **cardiac fibrosis**. ACE activity in the myocardium, but not in serum, was significantly increased in the rats with the banded aorta, and ACE immunoreactivity was increased in the areas of fibrosis. These changes were markedly reduced by both doses of imidapril. These results suggest that the increased local ACE expression contributes to the development of pressure overload-induced **cardiac fibrosis** but is not responsible for hypertrophy in rats.

L4 ANSWER 44 OF 83 MEDLINE on STN
ACCESSION NUMBER: 2004201032 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15098654
TITLE: KLF5/BTEB2, a Kruppel-like zinc-finger type transcription factor, mediates both smooth muscle cell activation and cardiac hypertrophy.
AUTHOR: Nagai Ryozo; Shindo Takayuki; Manabe Ichiro; Suzuki Toru; Kurabayashi Masahiko
CORPORATE SOURCE: Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine, Bunkyo-ku, Tokyo 113-8655, Japan.
SOURCE: Advances in experimental medicine and biology, (2003) 538 57-65; discussion 66.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
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AB Cardiac and vascular biology need to be approached interactively because they share many common biological features as seen in activation of the local renin-angiotensin system, angiogenesis, and extracellular matrix production. We previously reported KLF5/BTEB2, a Kruppel-like zinc-finger type transcription factor, to activate various gene promoters that are activated in phenotypically modulated smooth muscle cells, such as a nonmuscle type myosin heavy chain gene SMemb, plasminogen activator inhibitor-1 (PAI-1), iNOS, PDGF-A, Egr-1 and VEGF receptors at least in vitro. KLF5/BTEB2 mRNA levels are downregulated with vascular development but upregulated in neointima that is produced in response to vascular injury. Mitogenic stimulation activates KLF5/BTEB2 gene expression through MEK1 and Egr-1. Chromatin immunoprecipitation assay showed KLF5/BTEB2 to be induced and to bind the promoter of the PDGF-A gene in response to **angiotensin II** stimulation. In order to define the role of KLF5/BTEB2 in cardiovascular remodeling, we targeted the KLF5/BTEB2 gene in mice. Homozygous mice resulted in early embryonic lethality whereas heterozygous mice were apparently normal. However, in response to external stress, arteries of heterozygotes exhibited diminished levels of smooth muscle and adventitial cell activation. Furthermore, **cardiac fibrosis** and hypertrophy induced by continuous **angiotensin II** infusion. We also found that RARa binds KLF5/BTEB2, and that Am80, a potent synthetic RAR agonist, inhibits **angiotensin II**-induced cardiac hypertrophy. These results indicate that KLF5/BTEB2 is an essential transcription factor that causes not only smooth muscle phenotypic modulation but also cardiac hypertrophy and fibrosis.

L4 ANSWER 41 OF 83 MEDLINE on STN
ACCESSION NUMBER: 96254085 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8664344
TITLE: **Angiotensin II** induces TIMP-1 production in rat heart endothelial cells.
AUTHOR: Chua C C; Hamdy R C; Chua B H
CORPORATE SOURCE: Division of Geriatric Medicine, East Tennessee State University, Johnson City 37614-0429, USA.
CONTRACT NUMBER: HL 37011 (NHLBI)
SOURCE: Biochimica et biophysica acta, (1996 May 28) 1311 (3) 175-80.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960819
Last Updated on STN: 19980206
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AB **Angiotensin II** (AII) was found to upregulate tissue inhibitor of metalloproteineses-1 (TIMP-1) gene expression in rat heart endothelial cells in a dose and time-dependent manner. The maximal stimulation of TIMP-1 mRNA was achieved by 2 h after the addition of AII. This effect was blocked by losartan, an AT1 receptor antagonist and by calphostin C, a protein kinase C inhibitor. Addition of cycloheximide superinduced and actinomycin D abolished the induction. These results suggest that AII stimulates TIMP-1 production by a protein kinase C dependent pathway which is dependent upon de novo RNA synthesis. Immunoprecipitation experiment showed an enhanced band of 28 kDa from the conditioned medium of AII-treated cultures. Immunoblot analysis revealed that TIMP-1 was detectable in the conditioned medium 4 h after AII stimulation. Since endothelial cells line the blood vessels and sense the rise in AII associated with hypertension, the TIMP-1 released by these cells may provide an initial trigger leading to **cardiac fibrosis** in angiotensin-renin dependent hypertensi